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CORRESPONDENCE

Serologic response to mRNA COVID-19 vaccination in lymphoma patients

To the Editor:

The development of effective COVID-19 vaccines has been essential in slowing the spread of SARS-CoV-2. However, unvaccinated populations as well as those who do not respond to vaccination still remain at risk. Very few cancer patients were included in the COVID-19 mRNA vaccine trials and any individuals receiving chemotherapy or immunotherapy within 6 months were excluded.[1] Consequently, we have an inadequate knowledge of how well these vaccines work in the cancer patient population. However, by extrapolation from other vaccines, we hypothesized that patients with hematologic malignancies, especially those on immunosuppressive therapy, would produce poor serological responses to a COVID-19 vaccine.[2]

In this single-center, observational cohort study we assessed antibody responses in lymphoma patients receiving a COVID-19 mRNA vaccine (BNT162b2, BioNTech/Pfizer, Germany/New York, NY; or mRNA-1273, Moderna, Cambridge, MA). All patients provided written informed consent to participate in observational research, and this study was approved by the Weill Cornell Medicine institutional review board (IRB 21-02023288). Serum samples were obtained before (when possible) and after vaccination. Post-vaccination samples were collected within 11–70 days of the second dose (median 24.5 days). In the healthcare worker (HCW) control group, the post-vaccination samples were obtained within 10–68 days of the second dose (median 40 days) (-Figure S1). We also include data from a healthy control group of 35 HCWs enrolled in the NYP-WELCOME (WEilL COrnell Medicine Employees) observational trial (IRB 20-04021831). The use of this cohort in an mRNA vaccine study as well as the assay to quantify immunoglobulin G (IgG) antibodies to the SARS-CoV-2 S-protein has been described previously.[3] Additionally, we determined whether any patients had serum antibodies to the SARS-CoV-2 nucleocapsid (N) protein, a marker for prior infection.

The anti-S protein response to mRNA vaccination was assessed by enzyme-linked immunosorbent assay using sera from 67 patients with lymphoma and 35 healthy HCW controls. The majority of patients in this study were white (74.6%, Table S1). The median age of the study group was 71 (24–90). The most common comorbidities were hypertension (37.3%) and hyperlipidemia (50.7%). All patients were vaccinated with an mRNA vaccine (31 BNT162b2 and 36 mRNA-1273). The patients were categorized as having Hodgkin lymphoma (NHL; $n = 4$), chronic lymphocytic leukemia (CLL; $n = 21$), or other non-Hodgkin lymphomas ($n = 42$). Patients with other non-Hodgkin lymphomas included follicular lymphoma (7), marginal zone lymphoma (10), mantle cell lymphoma (8), diffuse large B-cell lymphoma (8), Waldenstrom macroglobulinemia (7), and other, unclassified lymphomas (2). No SARS-CoV-2 infections were identified during this study (February to April 2021).

The vaccine-induced IgG antibody responses to the SARS-CoV-2 S-protein are shown in Figure 1(A). The median and mean endpoint titers in the HCW control group were higher than in the lymphoma patients, although the difference was not significant. There were also no significant differences in mean titers when patients with different lymphomas were compared. However, while all 35 healthy control group members responded to the vaccine, a substantial proportion of the lymphoma patients did not. Thus, the anti-S endpoint titers in nine of the 21 CLL patients and 17 of the 42 other NHL patients were <10 000 (a cut-off level marked on Figure 1), and were often undetectable. By contrast, the four Hodgkin lymphoma patients all responded to the vaccines. When the data were grouped according to whether the participants received the BNT162b2 or mRNA-1273 vaccine, no differences were apparent.

In total, eight lymphoma patients were anti-N-positive while all members of the HCW control group were anti-N-negative. For four of the eight anti-N-positive lymphoma patients, there was evidence of COVID-19 prior to the start of this study. Thus, three patients had prior documented positive SARS-CoV-2 polymerase chain reaction (PCR) tests, while the fourth was not PCR-tested but later had a positive commercial antibody test. Seven of these eight anti-N-positive patients responded to vaccination. Taken together, anti-N-positive-lymphoma patients had significantly higher mean anti-S protein titers than their anti-N-negative counterparts ($p < 0.0001$) and the HCW group ($p = 0.02$). However, when anti-N-positive lymphoma patients were separated by treatment status (i.e., naïve, active therapy) the sample sizes were too small for comparisons to the anti-N-negative group.

We studied the CLL and other NHL patients in more detail to understand the implications of their treatment (Figure 1(B)). Every treatment-naïve and remote-therapy (no treatment in over 24 months) CLL patient responded to vaccination, whereas only 40% (6/15) of those currently being treated had anti-S protein titers above the designated cut-off value. A similar pattern was seen for the other NHL patients, although one individual in each of the treatment-naïve and remote-therapy groups failed to respond to the vaccine. Active therapy in this subgroup was again associated with a poor vaccine response, with only 21.4% (3/14) developing anti-S protein titers above the cut-off. The off-therapy subgroup, who had received treatment within 2 years but not at the time of vaccination, also had a lower vaccine response rate of 55.5% (5/9). The four non-

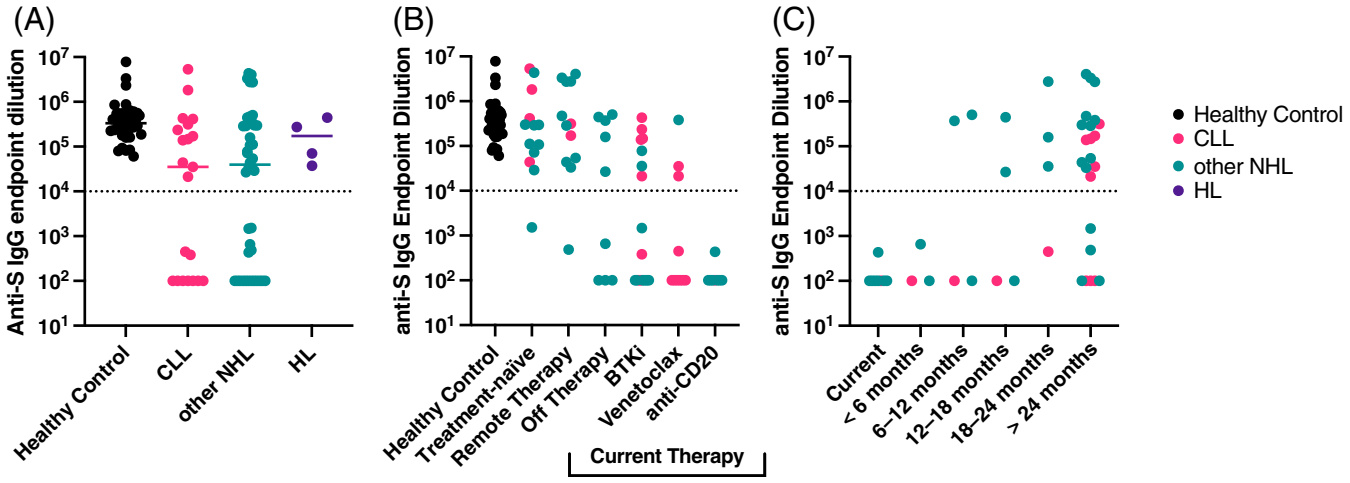

FIGURE 1 Anti-S immunoglobulin G (IgG) titers for healthy control and lymphoma patients. (A) SARS-CoV-2 S-protein antibody (anti-S IgG) endpoint enzyme-linked immunosorbent assay titers for healthy control ($n = 35$), chronic lymphocytic leukemia (CLL; $n = 21$), other non-Hodgkin lymphoma (NHL; $n = 42$), and Hodgkin lymphoma (HL; $n = 4$) patients. Blood samples were collected at least 11 days following inoculation with the second dose of an mRNA vaccine. The dotted line represents an endpoint anti-S protein titer (1:10000) that we judge to be an indicator of a strong response to vaccination. The short solid lines indicate the median titers for each group. There were no significant differences between the groups (unpaired, 2-tailed *t*-tests). (B) Anti-S IgG for CLL patients separated by treatment status and for the healthy control group. The treatment-naïve patients (CLL, $n = 4$; other NHL, $n = 9$) received no therapy at any time. The remote-therapy patients (CLL, $n = 2$; other NHL, $n = 10$) received no treatment within the 24 months prior to vaccination. The off-therapy patients (CLL, $n = 0$; other NHL $= 9$) received treatment within 24 months of vaccination but not during or after. Patients currently receiving therapy were treated as indicated: Bruton's tyrosine kinase inhibitor (BTKi: CLL, $n = 7$; other NHL, $n = 6$), venetoclax (CLL, $n = 9$; other NHL, $n = 1$), anti-CD20 therapy (CLL, $n = 1$; other NHL, $n = 7$). (C) Anti-S IgG titers for CLL and other NHL patients grouped by the time interval since anti-CD20 therapy ended. The "current" group was receiving anti-CD20 at the time of vaccination (CLL, $n = 1$; other NHL, $n = 7$). The other groups are designated according to how long therapy ceased before vaccination: < 6 months (CLL, $n = 1$; other NHL, $n = 2$); 6–12 months (CLL, $n = 1$; other NHL, $n = 3$); 12–18 months (CLL, $n = 1$; other NHL, $n = 3$); 18–24 months (CLL, $n = 1$; other NHL, $n = 3$); > 24 months (CLL, $n = 8$; other NHL, $n = 17$)

responders in this group had all received an anti-CD20 mAb within the previous 2 years; two within 6 months, one within 1 year, and one within 18 months. None of the patients currently on anti-CD20 mAb therapy seroconverted after vaccination.

We next studied the relationship between when anti-CD20 mAb therapy ceased and the vaccine response (Figure 1(C)). None of the 11 CLL and other NHL patients receiving this treatment within 6 months of vaccination had anti-S protein titers above the cut-off, but longer intervals were associated with higher titers. Thus, CLL and other NHL patients who were last treated >24 months before vaccination had response rates of 66.7% (6/9) and 71.4% (10/14), respectively. It is notable that 3/3 CLL and 3/4 other NHL non-responders in this subgroup were receiving a different type of active therapy at the time of vaccination (Table S6). We suggest that even when anti-CD20 mAb therapy ceased >24 months before vaccination, other forms of ongoing active therapy can compromise the vaccine response.

Thus we demonstrated that commonly used lymphoma therapies can adversely influence the performance of COVID-19 vaccines, with anti-CD20 mAbs having the greatest impact. With regard to anti-CD20 mAbs, our results are consistent with a growing number of reports that patients on active, or with recent anti-CD20 mAb treatment do not respond to vaccination.[4–6]

Compared with other studies, we report a higher rate of seroconversion in patients on active BTKi monotherapy.[4,5] Here, we found that 66.7% (4/6) of CLL patients and 50% (2/4) of other NHL patients did develop high-titer IgG antibodies after mRNA vaccination. In a study by Herishanu et al.[4] only 16% (8/50) of CLL patients treated with a BTKi responded to vaccination with BNT162b2. In our study, CLL responders on BTKi monotherapy were on treatment for a median length of 53.5 (23–74) months prior to the first vaccine dose. In comparison, CLL non-responders on BTKi monotherapy were on treatment for a median of 2 (1–3) months. The CLL responders were described as having a good response to BTKi monotherapy, with two patients in complete remission and two patients with no progression of disease. All CLL responders were compliant with treatment and only one patient had a recent interruption in therapy. This patient was hospitalized for COVID-19 in April 2020 and treatment was held for approximately 3 weeks after which therapy was restarted. In this study, he was found to be anti-N-positive, consistent with pre-existing serologic immunity from prior infection.

Finally, we studied the avidity of IgG antibodies to the Receptor Binding Domain in the lymphoma and healthy control patients (Figure S1). The avidity was significantly higher ($p < 0.0001$) for anti-N-positive lymphoma patients than for anti-N-negative lymphoma patients as well as healthy controls, all of whom were anti-N-negative (Figure S1(A)). These findings suggest COVID-19 convalescent patients (i.e., anti-N positive) have had longer to affinity mature their anti-S antibodies, which are boosted by the mRNA vaccines. We noted that patients currently receiving venetoclax or a BTKi had lower avidity S-protein antibodies than the other groups, although the group sizes were too small for statistical significance (Figure S1(B)).

In conclusion, we found that most lymphoma patients respond to vaccination with an mRNA-based COVID-19 vaccine, but a

substantial fraction (>40%) do not and therefore may remain at risk of infection and disease. There were no significant differences in the S-protein IgG antibody response rates or titers between the different lymphoma histologic subtypes. Treatment status was, however, a relevant variable. Treatment-naïve lymphoma patients responded to vaccination in a similar manner to the HCW group, as did patients who had not received therapy for at least 2 years. However, this controlled study presents compelling evidence that patients on active therapy for lymphoma may not respond to vaccination. Our results are particularly concerning for patients on anti-CD20 mAb therapy, given that no patients who had received treatment within 6 months responded well to mRNA vaccination. Thus these patients probably remain at risk of infection with SARS-CoV-2. In this patient population, we suggest exploring alternative strategies for protection such as passive immunization with anti-S monoclonal antibody therapy or, if possible, delaying therapy until after vaccination.

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CONFLICT OF INTEREST

PM has consulted for ADCT, AstraZeneca, Bayer, Beigene, BMS, Cellectar, Epizyme, Gilead, Janssen, Karyopharm, Merck, Regeneron, Takeda, Teneobio, and Verastem; and received research funding from Karyopharm. JPL has consulted for Sutro, Miltenyi, AstraZeneca, Epizyme, BMS/Celgene, Regeneron, Bayer, Gilead/Kite, Karyopharm, GenMab, Genentech/Roche, Abbvie, Incyte, and Janssen.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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